IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Ronald H. Chiarello *et al.*		
Serial No.:	09/894,423	Group No.:	1636
Filed:	6/28/01	Examiner:	Qian, C.
Entitled:	**Compositions and Methods for Labeling Oligonucleotides**		

DECLARATION OF DR. GABRIEL G. ALVARADO PURSUANT TO 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.10

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as Express Mail Label No.:EV769933213US and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: 08/14/2006

By: _____

Thomas W. Brown

Madam:

I, Dr. Gabriel G. Alvarado, under penalty of perjury, state that:

1. I am a joint inventor of the subject matter claimed in the United States patent application captioned above.

2. I am of one of skill in the art relevant to the patent application captioned above.

3. As noted in the application as filed,

> "[0007] In one embodiment, the present invention contemplates the use of a suitably protected and c*arefully selected set of amine linkers*, a modified deprotection/cleavage protocol and coupling methodologies *to allow for the convergent synthesis of any number of labeled oligonucleotides*. (emphasis added)

[0056] ... Conceptually, the approach consists of a *novel and empirically discovered modification* of the less popular two step procedure such that *both reactions are conducted on the solid phase support.* In Step 1, the fully protected support-bound oligonucleotide is reacted with linker phosphoramidite and the amino group is deprotected. In Step 2, the product is reacted with activated TMR, which has been produced *in situ* prior to addition. Cleavage and deprotection yield the desired oligonucleotide. (emphasis added)

[0057] This approach, while simple in concept, exhibits a number of significant advantages over the traditional approaches to DNA labeling. ... *Use of a common linker phosphoramidite with a variety of labeling compound* would greatly reduce such waste in a typical production environment. (emphasis added)

[0058] Further advantages are realized when one considers the required labor and the chemical difficulties ... and the need [in the art] to provide a variety of linker arms each of which is specific for certain applications." (brackets added)

4. The teachings, highlighted in paragraph 3 above, were the product of experimentation. These empirical data showed the inventors of the instant application that the two methoxy cyanoethyl moiety on the phosphate oxygen of the bifunctional linker, as recited in pending claims 1 and 4, facilitate the fidelity and efficiency of the *in situ* coupling reaction in the pending claims.

5. The linkers having a methyl group in U.S. patent 4,762,779 to Snitman cannot be substituted for the two methoxy cyanoethyl linkers described in the methods as claimed without a decrease in the efficiency and yields of these reactions as claimed.

6. Nothing in the teachings set out in U.S. patent 4,762,779 to Snitman and / or U.S. patent 6,255,476 to Vinayak *et al.* would suggest the use linkers, comprising CH_2CH_2CHN, which facilitate the reactions in the claimed embodiments of present invention.

Dated: 08/14/2006

Dr. Gabriel G. Alvarado